M. Gnidenko [1]
P. Vassiliev [1,2,3]
N. Gurova [1,2]
V. Muravyeva [1,2]

QUANTUM-CHEMICAL QSAR-MODELING OF NA^+/H^+ EXCHANGER 1 INHIBITORS BASED ON THE CONSENSUS OF NEURAL NETWORKS

[1] Chair of pharmacology,
[2] Research Institute of Pharmacology,
[3] Laboratory of Molecular Modeling and Computer Search for Drug Substances, Volgograd State Medical University, Pavshikh Bortsov square, 1, Volgograd, Russia

marina32_93@mail.ru

Na^+/H^+ exchanger type 1 (NHE1) promotes cell damage during ischemia and reperfusion. Therefore, the search for NHE1 inhibitors is a promising direction for creating new cytoprotective drugs. The first stage in the search for such inhibitors is the activity prediction*in silico*for novel chemical compounds.

The search for QSAR regularities was carried out based on the consensus of ensembles of artificial neural networks (ANN) using quantum-chemical parameters, for NHE1 inhibitory activity as an example.

The 78 new derivatives of cyclic guanidines (benzimidazoles and condensed benzimidazoles) were tested *in vitro*for NHE1inhibitory activity by the method[1].

For the constructing of decision rules, the following algorithm was implemented.

By k-means method three clusters were identified having different levels of activity: high, moderate, low. The atomic charges were calculated by AM1 method using Hyper Chem 8.0.

As descriptors (independent variables), the total charges of non-hydrogen atoms of 0-7 environment of the central carbon atom of the guanidine fragment Q_0– Q_7 were calculated [2]. The obtained data were used as input neuron signals.

Modeling of the neural network was carried out in the program Statistika 12 [3].The network architecture was a two-layer perceptron with a bottleneck.

The simulation was carried out in manual mode, with a pairwise exhaustive searchof the activation functions and the number of hidden neurons.The total number of types of simulated networks was 125.

During modeling, 5 variants of sampling with volumes of training-test-validation sets of 60-20-20% were assigned.

For each network, in each sampling variant (1 ... 5), 300 networks were constructed automatically (in three cycles of 100 networks).Best network was chosen by the user according accuracies for training, test and validation sets. For this best network, the prediction accuracy on the combined set was evaluated.

As a result, for each of the two binary gradations of activity ("high – not high", "high or moderate – not high or moderate"), 125 neural networks were obtained - 5 ensembles of 25 neural networks in each ensemble. When the prediction in the ensemble, the classification was made based on the average value of the confidential levels of the classifications in each ensemble of 25 networks.

The final prediction of the activitylevel of new compounds was carried out on the basis of a simple unweighted consensus of 5 ensemble estimates obtained in 5 ensembles.

For the expressed NHE1inhibitory activity, the following accuracy parameters were obtained on combined set: general accuracy (Fo), sensitivity (Fa), specificity (Fn).

Prediction accuracy parametersare: for individual ensembles Fo= 89.5%, Fa = 95.7%, Fn = 77.8%; for consensus Fo = 93.6%, Fa = 100%, Fn = 81.5%.

As a result, we can conclude, the consensus methodology for constructing QSAR regularities by neural networks based on the quantum-chemical variables was developed using the example of NHE1 inhibitors. Accuracy of consensus model exceeds the accuracy of individual neural network ensembles. The model may be used in the directed search for new NHE1 inhibitors.

1.Kusumoto K. et al. *British Journal of Pharmacology*, 2002,**135**: 1995-2003.
2. Vassiliev P.M. et al. *Journal of VolgSMU*, 2016, **2**: 87-90.
3. Statistica 12, *StatSoft, Inc.*, 2015,http://www.statsoft.com/.